

Amendments to and Listing of the Claims:

Please cancel claims 2-4, 7-9, 12 and 14, without prejudice or disclaimer. Please amend claims 1, 5, 6, 9, 10-17, without prejudice or disclaimer, and add a new claim 18, as set forth in the following listing of the claims, which will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A non-human transgenic animal selected from the group consisting of mice, rats, goats, pigs, sheep and cows, whose genome comprises:
~~a mammary-specific expression cassette system comprising:~~

~~(a) a foreign DNA sequence encoding a mature polypeptide which contains full coding region or recombinant gene structure;~~

~~(b) a second DNA sequence which is a secretion signal sequence preceding and operably linked to upstream of (a), said signal sequence encoding a secretional peptide, whereby said mature polypeptide is secreted of high levels into milk by said mammary gland cells;~~

~~(c) a third DNA sequence which is polyadenylation signal sequence preceding and operably linked to downstream of (a), said polyadenylation signal sequence can be recognized by poly(A) polymerase for polyadenylation tail editing, whereby said polyadenylation tail acts for stabilized the transgene mRNA molecules;~~

~~(d) a regulatory element of a gene encoding a milk protein of a mammary operably linked to the DNA sequences of (a), (b) and (c) above so as to form a hybrid gene which is expressible in the mammary gland of an adult lactating female of a transgenic animal whose genome comprises said hybrid gene; so that the mature polypeptide is secreted at detectable levels into milk of said mammal if said mammal is a lactating female.~~

(a) a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence;

(b) a nucleotide sequence encoding a signal peptide comprising bovine α -lactalbumin (α -LA) of SEQ ID NO: 13 or bovine α -S1 casein peptide of SEQ ID NO: 14, added to a N-terminal of the B-domain deleted human FVIII polypeptide of SEQ ID NO: 15; and

(c) an α -LA promoter;

wherein the B-domain deleted human FVIII polypeptide is secreted in milk when the non-human transgenic animal is lactating.

2. – 4. (Canceled)

5. (Currently amended) The non-human transgenic animal ~~whose genome comprises a mammary specific expression cassette~~ according to claim 1, wherein the signal peptide is ~~an artificial synthetic sequence as SEQ ID NO: 1 which obtained from the α bovine α -lactalbumin~~ α -lactalbumin signal peptide and created encoded by a DNA sequence of SEQ ID NO: 1 with a restriction enzyme, HpaI, cloning site in downstream of the DNA sequence of SEQ ID NO: 1.

6. (Currently amended) The non-human transgenic animal ~~whose genome comprises a mammary specific expression cassette~~ according to claim 1, wherein the signal peptide is ~~an artificial synthetic sequence as SEQ ID NO: 2 which obtained from the α bovine α -S1 casein~~ α -S1 casein signal peptide and created encoded by a DNA sequence of SEQ ID NO: 2 with a restriction enzyme, HpaI, cloning site in downstream of the DNA sequence of SEQ ID NO: 2.

7. – 9. (Canceled)

10. (Currently amended) The non-human transgenic animal according to claim ~~3~~ 1, wherein ~~said the~~ nucleotide sequence encoding the B-domain deleted human FVIII polypeptide comprises a light chain (A3-C1-C2 domain) and a heavy chain (A1-A2 domain) and ~~wherein said the~~ light chain and heavy chain are operably linked by a junction.

11. (Currently amended) The non-human transgenic animal according to claim 9, wherein ~~said~~ the mammary gland-specific signal peptide sequences ~~are~~ SEQ ID NO: 13 and SEQ ID NO: 14 for 19 residue of alpha lactalbumin and 15 residue of alpha-S1 casein signal peptides, respectively comprises at least one of the bovine α -lactalbumin of SEQ ID NO: 13 with 19 amino acid residues and the bovine α -S1 casein peptide of SEQ ID NO: 14 with 15 amino-acid residues.

12. (Canceled)

13. (Currently amended) A method for ~~producing the~~ making the non-human transgenic animal of claim 1 comprising the steps of:

a.i. introducing into a mammalian an embryo at least one expression cassette system comprising a DNA sequence encoding a mature polypeptide which intact human FVIII or B domain-deleted human FVIII operatively linked to mammary gland-specific regulatory sequences of the non-human transgenic animal a transgene whose genome comprises (a) a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15, wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland-specific signal peptide sequence; (b) a nucleotide sequence encoding a signal peptide comprising bovine α -lactalbumin (α -LA) of SEQ ID NO: 13 or bovine α -S1 casein peptide of SEQ ID NO: 14, added to a N-terminal of said B-domain deleted hFVIII polypeptide of SEQ ID NO: 15, and (c) an α -LA promoter; and

b.ii. implanting the embryos-embryo into a female of the same species of the non-human transgenic animal;

iii. permitting the embryo to develop to full term; and

iv. identifying these the non-human transgenic animal producing mammals which produce in their milk that contains a detectable quantities of a mature polypeptide

~~which intact human FVIII or~~ quantity of the B domain-deleted human FVIII
polypeptide.

14. (Canceled)

15. (Currently amended) The method ~~for producing the transgenic animal~~ according to claim 13, wherein ~~a plurality of different~~ the transgene is presented in an expression cassettes ~~are~~ cassette that is introduced and these cassettes to the animal to express at least two different ~~mature polypeptides which intact human FVIII and~~ the B domain-deleted human FVIII polypeptide.

16. (Currently amended) The method ~~of~~ according to claim 13, wherein the expression level of the human FVIII in the milk of ~~said the non-human transgenic animals can reach~~ animal is about 50 mg/L, and its the human FVIII has a clotting activity can reach about 13-fold higher than that of a clotting activity of human FVIII in normal human plasma.

17. (Currently amended) The method ~~of~~ according to claim 13, wherein ~~the a~~ a purified human FVIII from the transgenic milk can be applied for of the non-human transgenic animal is applicable to a supplementary therapy used.

18. (New) The non-human transgenic animal according to claim 1, wherein the α -LA promoter is a 2.0-kb bovine α -LA promoter.